AMENDMENT TO THE CLAIMS

1. (**Currently Amended**) A method for engineering a spatially conserved protease motif into a recipient polypeptide that binds a target, the method comprising:

   a) obtaining a spatial relationship for a first set of amino acid residues of the spatially conserved protease motif, said protease motif comprising 2, 3, 4, 5, 6, 7, or 8 amino acid residues,

   b) identifying a second set of amino acid residues in the recipient polypeptide, wherein said second set of amino acid residues have a geometric relationship that matches the spatially conserved geometry of the protease motif, and wherein the recipient polypeptide binds to a target that is an extracellular signaling molecule,

   c) substituting said second set of amino acid residues in said recipient polypeptide with the first set of amino acid residues making up said protease motif, and,

   d) expressing and testing for ~~catalytic activity~~ protease activity of the recipient polypeptide substituted with the first set of amino acid residues making up said protease motif,

   thereby engineering the spatially conserved protease motif into the recipient polypeptide.

2. (**Canceled**)

3. (**Original**) The method of claim 1, wherein the targeted extracellular signaling molecule is an inflammatory cytokine.

4. (**Original**) The method of claim 1, wherein the targeted extracellular signaling molecule is TNF-α.

5. (**Previously Presented**) The method of claim 1, wherein the recipient polypeptide is: a binding portion of an anti-TNF-α antibody, a soluble ligand binding portion of a TNF-α receptor, or a TNF-α polypeptide.

6. (**Canceled**)

7. (**Previously Presented**) The method of claim 1, wherein the protease motif comprises a serine protease triad.

8. **(Previously Presented)** The method of claim 1, wherein said second set of amino acid residues identified in said recipient polypeptide are less than about 10Å away from a target binding site.

9. **(Previously Presented)** The method of claim 1, further comprising, before step (d), constructing a model of said recipient polypeptide containing said first set of substituted amino acid residues *in silico*, and determining the existence of atomic clashes between atoms in said model.

10. **(Original)** The method of claim 9, wherein the model is rejected if atomic clashes are present between atoms in said model.

11. **(Previously Presented)** The method of claim 1, further comprising, before step (d), constructing a model of said recipient polypeptide containing said first set of substituted amino acid residues *in silico*, and comparing the polypeptide backbone of said recipient polypeptide in the presence and absence of said first set of substituted amino acid residues.

12. **(Previously Presented)** The method of claim 11, further comprising, before step (d), determining the root mean squared deviation of α-carbon atoms in said polypeptide backbone in the presence and absence of said first set of substituted amino acid residues.

13. **(Original)** The method of claim 12, wherein the model is rejected if there is a root mean squared deviation of greater than 2Å between backbone α-carbon atoms.

14. **(Canceled)**

15. **(Previously Presented)** The method of claim 1, wherein identifying said second set of amino acid residues in the recipient polypeptide includes modeling the presence of a β-carbon on a glycine residue of the recipient polypeptide.

16. **(Previously Presented)** The method of claim 15, wherein said second set of amino acid residues in said recipient polypeptide comprise a glycine residue.

17-20. **(Canceled)**

21. **(Currently Amended)** A method for engineering a spatially conserved protease motif into a recipient polypeptide, the method comprising:

a) obtaining a spatial relationship for a first set of amino acid residues of the spatially conserved protease motif, said protease motif comprising 2, 3, 4, 5, 6, 7, or 8 amino acid residues;

b) identifying a second set of amino acid residues in the recipient polypeptide, wherein said second set of amino acid residues have a geometric relationship that matches the spatially conserved geometry of the spatially conserved protease motif, and wherein identifying said second set of amino acid residues in the recipient polypeptide includes modeling the presence of a β-carbon on a glycine residue of the recipient polypeptide;

c) substituting said second set of amino acid residues in said recipient polypeptide with the first set of amino acid residues making up said protease motif; and,

d) expressing and testing for ~~catalytic activity~~ protease activity of the recipient polypeptide substituted with the first set of amino acid residues making up said protease motif,

thereby engineering the spatially conserved protease motif into the recipient polypeptide.

22. (**Original**) The method of claim 21, wherein the recipient polypeptide binds to a target molecule.

23. (**Previously Presented**) The method of claim 22, wherein the target molecule is an extracellular signaling molecule.

24. (**Original**) The method of claim 23, wherein the extracellular signaling molecule is TNF-α.

25-26. (**Canceled**)

27. (**Previously Presented**) The method of claim 21, wherein the protease motif comprises a serine protease triad.

28. (**Previously Presented**) The method of claim 21, wherein said second set of amino acid residues identified in said recipient polypeptide are less than about 10Å away from a target binding site.

29. **(Previously Presented)** The method of claim 21, further comprising, before step (d), constructing a model of said recipient polypeptide containing said first set of substituted amino acid residues *in silico*, and determining the existence of atomic clashes between atoms in said model.

30. **(Original)** The method of claim 29, wherein the model is rejected if atomic clashes are present between atoms in said model.

31. **(Previously Presented)** The method of claim 21, further comprising, before step (d), constructing a model of said recipient polypeptide containing said first set of substituted amino acid residues *in silico*, and comparing the polypeptide backbone of said recipient polypeptide in the presence and absence of said first set of substituted amino acid residues.

32. **(Previously Presented)** The method of claim 31, further comprising, before step (d), determining the root mean squared deviation of α-carbon atoms in said polypeptide backbone in the presence and absence of said first set of substituted amino acid residues.

33. **(Original)** The method of claim 32, wherein the model is rejected if there is a root mean squared deviation of greater than 2Å between backbone α-carbon atoms.

34. **(Canceled)**

35. **(Previously Presented)** The method of claim 21, wherein said second set of amino acid residues in said recipient polypeptide comprise a glycine residue.

36-55. **(Canceled)**

56. **(Currently Amended)** A method for engineering a spatially conserved partial protease motif into a target binding recipient polypeptide or polypeptide complex, the method comprising:

a) obtaining a spatially conserved residue geometry for a spatially conserved protease motif, said protease motif comprising 2, 3, 4, 5, 6, 7, or 8 amino acid residues;

b) identifying a set of amino acid residues in a holo-complex comprising the recipient polypeptide or polypeptide complex, and the target, wherein said set

of residues have a geometric relationship that matches the spatially conserved geometry of the motif, and wherein at least one of said amino acid residues of the set occur in the target;

c) identifying in the set of amino acid residues a subset of amino acid residues that are present on the recipient polypeptide or polypeptide complex;

d) substituting the subset of residues in said recipient polypeptide or polypeptide complex with the corresponding amino acid residues of said motif; and,

(e) expressing and testing for ~~catalytic activity~~ protease activity of the recipient polypeptide or polypeptide complex substituted with the corresponding amino acid residues of said protease motif,

thereby engineering the partial protease motif into the recipient polypeptide or polypeptide complex, such that binding of the engineered recipient polypeptide or polypeptide complex to the target reconstitutes the protease motif.

57-68. **(Canceled)**